IN VITRO AND IN VIVO STUDIES ON THE IMPORTANCE OF THE SOLUBLE GUANYLYL CYCLASE ALPHA 1 SUBUNIT IN PENILE ERECTION

Decaluwe[1] K., Nimmegeers[1] S., Thoonen[2,3] R., Brouckaert[2,3] P., Van de Voorde[1] J.

[1]*Department of Pharmacology, Ghent University, Ghent, Belgium*
[2]*Department for Molecular Biomedical Research, VIB, Ghent, Belgium*
[3]*Department of Biomedical Biology, Ghent University, Ghent, Belgium*

Penile erection is a highly regulated physiologic event in which the NO-cGMP pathway plays a pivotal role. In the corpora cavernosa, NO is synthesized by both neuronal NOS and endothelial NOS. Independent of its source, NO diffuses to the arterial and corporal smooth muscle cells for binding its target sGC. This enzyme is responsible for the catalyzation of GTP to cGMP. After activation of sGC by NO an increase in cGMP occurs which results in a cascade of events eventually leading to smooth muscle relaxation and penile erection. So sGC plays a key role in the mechanism of erection and seems to be an attractive and promising new target for the treatment of erectile dysfunction. In its molecular make-up, sGC is a heterodimer consisting of an α and a β subunit. Of both subunits, two isoforms have been characterised, however only the $sGC\alpha_1\beta_1$ and $sGC\alpha_2\beta_1$ heterodimers are functionally active. In order to elucidate the functional role of the $sGC\alpha_1\beta_1$ heterodimer in the mechanism of erection, experiments were performed in vivo and on isolated corpora cavernosa using

$sGC\alpha_1^{-/-}$ mice. For the in vivo study sGC-dependent and –independent vasorelaxing agents were injected intracavernosally and the rise in intracavernosal pressure was recorded in $sGC\alpha_1^{-/-}$ mice and their littermates. For the in vitro study isolated corpora cavernosa tissues from $sGC\alpha_1^{-/-}$ mice and their littermates were mounted in organ baths for isometric tension recording. When a stable contraction was achieved by administration of 5 µmol/L norepinephrine, concentration-dependent curves were obtained for different sGC-dependent and –independent vasorelaxing agents. These studies were conducted on 2 different mice strains (129SvEvS7 and C57BL6/J) to determine potential stain differences. The responses in $sGC\alpha_1^{-/-}$ to administration of SNP (1 - 4 µg/kg or 10^{-9}– 10^{-5} mol) and spermine-NO (10 - 20 µg/kg or 10^{-9}– 10^{-5} mol) and to EFS (1 - 8 Hz, 80V, 20s) or stimulation of the nervus cavernosus (5 - 15 Hz, 8V, 60s) are significantly reduced although not completely abolished, illustrating the importance of the $sGC\alpha_1\beta_1$ heterodimer. However this study also provides evidence that activation of $sGC\alpha_1\beta_1$ is not the sole mechanism responsible for penile erection.